A STUDY OF INTESTINAL TUBERCULOSIS WITH PARTICULAR REFERENCE TO RISK FACTORS

A dissertation submitted in part fulfillment of the requirements for DM (Branch IV, Gastroenterology) examination of the Tamil Nadu Dr. M.G.R. Medical University, Chennai to be held in February 2007.

CERTIFICATE

This is to certify that that this dissertation entitled "**A study of intestinal tuberculosis with particular reference to risk factors**" is the bonafide work done by Dr. Suresh Shenoy in partial fulfillment of rules and regulations for DM (Branch IV Gastroenterology) examination of the Tamil Nadu Dr. M.G.R. Medical University, Chennai to be held in February 2007.

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HISTORY:

Tuberculosis has been present in humans since antiquity. The origins of the disease are in the first domestication of cattle. Skeletal remains show prehistoric humans (4000 BC) had TB, and tubercular decay has been found in the spines of Egyptian mummies from 3000-2400 BC. There were references to TB in India around 2000 BC.

Around 460 BC, Hippocrates called the disease phthisis (consumption), emphasizing the dramatic aspect of general wasting associated with chronic untreated cases. He described that diarrhea in a patient with phthisis is a mortal symptom.

Around 200 A.D., the Roman doctor Claudius Galen recognized the consumption as incurable and recommended a treatment plan of fresh air, rest, and good food.

Results of postmortem examination on Louis XVIII evidenced an ulcerative lesion with intestinal perforation associated with a cavitary lung disease.

In 1546, Girolamo Tracastoro explained the contagious nature of TB in his book "De Morbis Contagiosis". He wrote that bed sheets and clothing could contain contagious particles.

In 1679, Franciscus de la Boe, more commonly known as Dr. Silvius, wrote the "Opera Medica". He described the tubercles and characterized the infection's course throughout the lungs and body of infected patients providing clear descriptions detailing the tuberculous cavities and tuberculous lymph nodes as well.

In 1720, an English physician, Benjamin Marten, was responsible for the first theory regarding Mycobacterium tuberculosis as "wonderfully minute living creatures". He wrote the book "A New Theory of Consumption*"* regarding his views.

In 1761, Austrian Leopold Avensbrugger wrote a book on tuberculosis about the clinical symptoms and different pathologies of the disease.

In 1782, a physicist named Graumann proved conclusively that syphilis and tuberculosis were not the same disease.

In1810, a London physician, Carmichael, wrote a dissertation demonstrating that cattle tuberculosis is transmitted to humans through infected meat and milk.

In1854, Hermann Brehmer who suffered from TB himself theorized that TB was treatable after his doctor recommended that he move to a more temperate climate, like the Himalayas. After recuperating there, he returned home healthy and cured. He built the first sanatorium where patients could recuperate under the influences of fresh air and healthy eating habits.

In 1865, a French army physician, Jean-Antoine Villemin demonstrated the transmission of TB from humans to cattle to rabbits. He theorized that the disease was caused by a certain organism and did not arise from spontaneous generation as previously believed.

In March 24, 1882 Robert Koch identified and described the bacillus-causing tuberculosis, Mycobacterium tuberculosis. He received the Nobel Prize in physiology or medicine in 1905 for this discovery. Koch did not believe that bovine (cattle) and human

tuberculosis were similar, which held back the recognition of infected milk as a source of infection. Later, this source was eliminated by the pasteurization process. Koch announced a glycerin extract of the tubercle bacilli as a "remedy" for tuberculosis in 1890, calling it 'tuberculin'. It was not effective, but was later adapted by von Pirquet in a test for pre-symptomatic tuberculosis.

BCG (Bacillus of Calmette and Guerin) was developed from attenuated bovine-strain tuberculosis by Albert Calmette and Camille Guerin in 1906. The BCG vaccine was first used on humans on July 18, 1921 in France.

In 1890, an Italian doctor, Forlanini, created the first therapy for TB patients. He found that collapsing the lungs had positive effects on recovery from tuberculosis.

In 1895, Wilhelm Konrad bon Rontgen used radiation to examine the progression and assess the severity of the illness in TB patients.

In1920s, a treatise by Assmann cultivated the theory of reinfection.

Finally, in 1943, Selman A. Waksman developed the antibiotic Streptomycin. The first time it was administered to a live, human patient was November 20, 1944. The progression of the disease was halted, the bacteria were later absent from the sputum, and the patient was fully healed. In the years following, more TB drugs were discovered.

Hopes that the disease could be completely eliminated have been dashed since the rise of drug-resistant strains in the 1980s. The resurgence of tuberculosis resulted in the declaration of a global health emergency by the World Health Organization in 1993.

INTRODUCTION:

Tuberculosis (TB) remains the single largest infectious disease causing high mortality in humans, leading to 3 million deaths annually, about five deaths every minute. Approximately 8-10 million people are infected with this pathogen every year[12]. In India, there are about 500,000 deaths occurring annually due to TB[13], with the incidence and prevalence being 1.5 and 3.5 millions per year.

Approximately two billion individuals globally are infected with Mycobacterium tuberculosis, yet only 10% develop clinical tuberculosis [1].There was a surge of tuberculosis in mid-1980s in developed countries which may be due to multiple factors like infection with human immunodeficiency virus (HIV), immunosuppression with prolonged steroid therapy, immigration from countries with high prevalence of tuberculosis, and social problems such as poverty, homelessness, and drug abuse [2, 3].

Tuberculosis continues to be a major health problem in India [4, 5]. Deaths due to tuberculosis accounts to around 50/100,000 population. Forty percent of the cases in India contract tuberculosis by the age of 6 years and 80% by the age of 16 years [6]. The incidence of tuberculosis is also increasing in Western countries [7, 8, 9]. Poor socio economic status, poor sanitation and recent upsurgence of HIV infection enhance the susceptibility to tuberculosis in India. The exact prevalence of intestinal tuberculosis in India is not known.

Several susceptibility-associated genetic polymorphisms have been proposed to explain differential susceptibility to tuberculosis (TB) progression in different populations. Though several gene polymorphisms have been associated with susceptibility or resistance to TB in different ethnic populations, only few of these genetic associations have shown to have functional effect on the containment by the host immune system.

REVIEW OF LITERATURE:

Intestinal tuberculosis (ITB) was common in the early 20th century. It was responsible for most cases of small intestinal obstruction and stricture. There was a decline in ITB cases in the middle of the century in developed countries which was caused by 1) an increased standard of living 2) pasteurization of milk 3) control of bovine tuberculosis through slaughter of reactive animals and 4) the introduction of antituberculous chemotherapy in the 1950s.

Gastrointestinal tract (GIT) is a common location for tuberculosis infection and is the sixth most frequent site of extra pulmonary involvement. Intestinal tuberculosis still remains the most common granulomatous disease of the bowel in India [10, 11]. Intestinal tuberculosis is an important cause of morbidity in the Indian population, especially because the diagnosis is often delayed due to non-specific nature of its signs and symptoms.

The incidence in hospital admissions for ITB has been reported to be 0.8%[4]. In India, TB is responsible fir 7% of hospital admissions for intestinal obstructions and 6% of perforations[21]. Any segment of the GIT can be involved by tuberculosis, but the ileocecal region is the most commonly involved part of the tract, noted in up to 90% of cases with intestinal tuberculosis[14, 15, 29, 30.] In India, the organism isolated from all intestinal lesions has been Mycobacterium tuberculosis and not Mycobacterium Bovis [16,17,18,19] .In Bhansali's series[4], including 196 patients with gastrointestinal tuberculosis, ileum was involved in 52% and cecum in 51% of cases. Of the 300 patients in a study, ileocecal involvement was present in 54% of cases[20]. The frequency of bowel involvement declines as one proceeds both proximally and distally from the ileocecal region.

ITB is thought to result from swallowed organisms (infected sputum in active pulmonary tuberculosis or ingestion of contaminated milk) that directly penetrate the intestinal mucosa. Hematogenous spread (active pulmonary tuberculosis, miliary TB, or silent bacteremia during primary phase of TB) and direct extension from adjacent organs can also occur. Although any area of the GIT can be involved, the ileocaecal region is involved in approximately 75% of cases and studies in India have suggested that approximately 20% of the patients may have associated pulmonary involvement [22]. It has been estimated that only 10% of persons infected with Mycobacterium tuberculosis will ever develop clinical disease. Of the total number of patients with TB, only about 1% will have intestinal disease.

Socioeconomic and environmental factors have long been known to influence the occurrence of tuberculosis in a community. A survey carried out in Wardha district (Maharashtra) is the only source of survey data (unpublished) linking tuberculosis in the community to socio-economic criteria [23]. The prevalence rates in the survey had depended on literacy (lowest in the graduates and highest among the illiterates) and present employment (highest among the professionals, followed by cultivators and agricultural labour). These had also depended on income, living standard (those living in "Kutcha" houses had a higher prevalence than "pucca" house dwellers). Of the total cases in women, 48 percent were among those unemployed (include housewives). For all demographic variables, rates in female were less than those in males.

As per Dholakia [24], evidence is lacking to assume a differential prevalence rate of tuberculosis among workers than among non-workers. Of the 'workers' group, estimated to be suffering from tuberculosis in India, about 52 percent were in the age group 15- 44 years. In this age group, women constitute about 40 percent and 17.9 percent of the workers with

tuberculosis in the urban and rural areas respectively. There was much lower proportion of women among workers with tuberculosis in higher ages, especially in the urban areas. In the Wardha survey [23], the urban professionals and rural service workers, who had a higher prevalence, had a low proportion of the female population in them, and had consequently accounted for a small proportion of the total cases among females. The extent of tuberculosis morbidity in the males in the economically active age and in females in the reproductive age marks it out as a priority among the public health problems in India.

The available literature strongly suggests the possible role of genetic factors in the control of host responses to Mycobacterium tuberculosis (M.TB) [25, 26]. Stead [27], has proposed that susceptibility to infection with M. TB has changed from being the norm of all humans to being an infection of certain population as a result of natural selection of resistance among ancestors who came in contact with the bacterium and survived the illness during the preantibiotic era. Distinct environmental and natural selective factors have likely resulted in population – specific immunogenetic adaptations to clinical tuberculosis.

Convincing evidence exists from twin studies that host genetic factors are important in determining susceptibility to the infection. Kallmann and Reisner[28] found an appreciably high concordance of pulmonary TB in monozygotic than dizygotic twins. Also the aggregation of pulmonary tuberculosis in families emphasizes the importance of heredity.

The different manifestations of infection with M.TB reflect the balance between the bacilli and host defense mechanisms. Traditionally, protective immunity to tuberculosis has been ascribed to T-cell-mediated immunity, with $CD4^+$ T cells playing a crucial role. Recent immunological and genetic studies support the long-standing notion that innate immunity is also relevant in tuberculosis.

There are several evidences to suggest that the production of the human leukocyte antigen (HLA) system, the major histocompatibility complex of humans, have an important function in controlling the cellular immune response to infectious agents[31]. Though cellular immunity in TB is regulated by HLA system, the exact role of HLA –DR genes on both the development and course of TB, as well as cellular and humoral immune response remains unknown. It is possible that the gene products are involved in the activation of T helper and inducer cells rather than in subsequent T-cell activation of B cells. Singh et al [32] showed that the DR2 antigen had a preferential tendency to be transferred from TB parents to their affected children. In a group of pulmonary TB patients from North India, he found that TB patients had an increased frequency of DR2 antigen and a marked decrease of DRW6 in comparison to healthy subjects. In a group of pulmonary TB patients from South India, Brahmajyothi V et al [33] noted that the frequencies of HLA-A10 and B8, but not DR2 were greater in control subjects. Hence DR2 may be involved in the pathogenesis of advanced pulmonary tuberculosis. The MHC genes may be physically close to the chromosome region that carries a gene conferring susceptibility or resistance to a particular disease. This association may explain the lack of complete association and geographic variation, due to linkage disequilibrium. Though HLA –DR2, DQ1 and their subtypes are significantly associated with the susceptibility to tuberculosis, and they may not be the sole genetic markers predisposing to tuberculosis suggesting that non-HLA genes may have a role in infection.

M.TB is an intracellular parasite and cell mediated immunity is crucial for containment of infection[34]. After macrophage stimulation by mycobacterial infection, the secretion of TNF-α, interleukin-12, and possibly other factors by macrophages promotes

interferon-γ secretion by natural killer cells, differentiation of antigen-driven CD4+ T cells into interferon-γ producing Th1 cells, and activation of these Th1 cells to secrete interferon-γ and possibly other macrophage-activating factors[35]. Secretion of interferon-γ, in turn, results in macrophage secretion of TNF-α; enhanced antigen presentation, activation of macrophage mycobactericidal mechanisms such as nitric oxide production; and impaired proliferation of interleukin-4–secreting Th2 cells.

Interferon-γ induces cellular activation by binding to a receptor complex consisting of at least two subunits: the interferon-γ binding subunit (interferon-γ receptor 1) and a chromosome 21–encoded transmembrane accessory factor (interferon-γ receptor 2). Both components of the receptor are thought to be required for normal signal transduction. Binding of interferon-γ induces dimerization of the interferon-γ receptor 1, which subsequently associates with interferon-γ receptor 2. Interferon-γ interacts with both interferon-γ receptor 1 and interferon-γ receptor 2 during the process of association of the two-receptor proteins[36]. The Janus protein kinases Jak 1 and Jak 2 are associated with the intracellular domains of interferon-γ receptor 1 and interferon-γ receptor 2, respectively, and are brought together and activated by phosphorylation by the binding of interferon-γ to the receptor complex. This results in the phosphorylation of tyrosine at position 457 of the interferon-γ receptor 1 chain and produces a binding site for Stat 1 α (signal transduction and activation of transcription protein), leading to the phosphorylation, homodimerization, and subsequent dissociation of Stat 1α from the interferon-γ –receptor complex. The Stat 1α dimer translocates to the nucleus and interacts with γ– activation sequences in the promoter regions of interferon-γ – inducible genes, resulting in their transcription.

Activation of infected macrophages by interferon-gamma (IFN-γ) derived from T cells and natural killer cells are the principal antimycobacterial effector mechanisms. The importance of IFN-γ in human mycobacterial immunity was established by the identification of mutations in the gene encoding the IFN-γ receptor ligand binding chain as a cause of susceptibility to mycobacterial infection [37, 38].

Recently several studies have shown that genes coding for different cytokines may affect host susceptibility to tuberculosis. Interferon-gamma (IFN-γ) is a proinflammatory Th1-type cytokine produced by T cells that appears to be necessary for the containment of mycobacterial infections. IFN-γ knockout mice were found to be highly susceptible to infection with M.TB. A recent study[39]demonstrated association between the (+874 A /T) polymorphism in the IFN-γ gene and pulmonary TB, with subjects lacking the T allele was found to be at risk for pulmonary and meningeal tuberculosis. In a Spanish population, patients who were homozygous for the (+874A) allele of IFN-γ had a 3.75 fold increased risk of developing compared to healthy controls[64]. Reports have shown that a complete deficiency of interferon-γ receptor 1 may lead to BCG infection in vaccinated children or to atypical mycobacterial infection in unvaccinated persons[38].

Although IFN-γ production may vary among subjects, some studies suggest that IFN-γ levels are depressed in patients with active TB [40, 41.] In a study comparing the immune response to pre and post- BCG vaccination, it was seen that BCG had little effect in driving the immune response towards IFN-γ and a protective Th1 response[42]. In a study done to determine whether the effect of balance of T cell cytokines during initial stages of infection on clinical manifestations with M. TB in children, it was found that IFN-γ production was

most severely depressed in patients with moderately advanced and far advanced pulmonary disease and in malnourished patients though production of IL-12, IL-4 and IL-10 was similar in TB patients and healthy tuberculin reactors. Hence it is found that polymorphisms in the genes of these cytokines have functional significance[43].

Several polymorphic-derived deletions and point mutations of the mannose–binding lectin (MBL) [44-48], human analogue of the murine natural resistance associated macrophage protein 1 (NRAMP1) gene [49-53], the vitamin D receptor (VDR) gene [54-55], the interleukin -1 (IL -1 α and ß) [56-58], IL -1 receptor antagonist (IL-1RA) [58,59,60], IL-10 [56,61], IL -12 receptor antagonist (IL-12R) [62], tumor necrosis factor- alphą and beta (TNF-α and ß) [56,63], interferon-γ [39,64]and interferon-γ receptor 1[38] genes have been associated with susceptibility or resistance to TB in different ethnic groups. Only few of these genetic associations have been shown to have relevant functional impact on the containment of the bacteria by the host immune system.

Besides genetic differences in Th1/Th2 responses, conditioning of the mucosal immune system in childhood may be important in determining susceptibility to ITB. It has been postulated that helminthic infections (associated with less domestic hygiene) may stimulate a Th2-type immune reaction, down-regulate IFN-γ, and increase susceptibility to tuberculosis [65, 66].

Association of important candidate gene variants of HLA and non-HLA genes with the susceptibility or resistance to pulmonary tuberculosis in Indian population[72]

Candidate genes	Effect	Reference
HLA HLA-DR2	 Susceptibility	 32,33,73
Sub-type -DRB1 * 1501, * 1502 -DRB1 * 1501	 Susceptibility Susceptibility	 74 75.76
HLA-DQ1 - DQB1*0601	Susceptibility Susceptibility	73.75 75
HLA-DP -DPB1*02	Susceptibility	75
Haplotype: DRB1and1501- DQB1*0601 DRB1 * 11(5) DRB1 * 10 DQB1*0501	 Susceptibility Resistance Resistance Resistance	 75 75 75 75
Non-classical HLA Transporter Associated with Antigen Processing (TAP) gene TAP 2 and DR2.	Susceptibility	77
Non-HLA Functional mutants Homozygotes to Mannose Binding Lectin (MBL) gene (codon 52,54 and 57) - Heterozygotes of MBL codon 57 Vitamin D receptor (VDR) gene variants (Bsml, Apal, TaqI and FokI) NRAMP1 [(CA) n 823C/T, TGTG+/del and D543N G/A]	 Susceptibility Resistance to bacteriological relapse Differential susceptibility and resistance in males and females No association with susceptibility or resistance	 47 47 60,78 79
Cytokine gene TNF- α -238, -308 TNF- ß	 No association No association	 63 63
Haplotypes HLA-B17- TNF-α -238/A HLA-B17- TNF-α -308/2 HLA-B17- TNF- ß -2	 Associated with bacteriological relapse	 63

Tuberculosis in HIV:

Extrapulmonary disease is more common in patients with AIDS; 50% of the AIDS patients with tuberculosis have extrapulmonary involvement compared to only 10-15% of non-HIV tuberculosis patients [67]. While 10 percent of those infected with TB will progress to active disease over their life times, those who are co-infected with both TB and HIV on the other hand progress rapidly, at the rate of 10 percent annually and about 60 percent in their life time. The pathogenesis of TB can be altered by HIV either through reactivation of latent tuberculosis infection to active disease (more common) or by causing rapid progression from recent infection with M. TB to tuberculosis disease. With progression of HIV infection, CD4+ T-lymphocytes decline in number and function. The immune system is therefore, less able to prevent the growth and local spread of M.TB. As a result, disseminated and extra-pulmonary disease is more commonly seen. Nevertheless, pulmonary TB is still the most common form of TB even in HIV infected patient; pulmonary involvement can occur in 70-90 percent of all patients with TB [68].

Tuberculosis may precede the diagnosis of Acquired immunodeficiency syndrome (AIDS) by few months and the disease may be severe and progress rapidly in AIDS and vice versa [69, 70]. Multidrug resistant TB is more common in patients with AIDS[71].The risk of tuberculosis infection progressing to active tuberculosis is estimated to be 8 percent per year in an HIV positive person, as opposed to 10 percent life time risk in an immunocompetent person, infected with tuberculosis (non-HIV) [68].

PATHOPHYSIOLOGY:

The pathophysiology of intestinal tuberculosis has been attributed to four mechanisms[80]: 1) swallowing of infected sputum in patients with active pulmonary TB; 2) hematogenous spread from active pulmonary or milary TB; 3) ingestion of contaminant milk or food; 4) contiguous spread from adjacent organs. After the tubercle bacillus enters the gastrointestinal tract, it traverses the mucosa to lodge in the submucosa. There, the presence of the bacillus induces inflammatory changes, including serosal and submucosal edema, cellular infiltration, and lymphatic hyperplasia. Eventually appearance of granulomas causes small papillary mucosal elevations[81]. Lymphangitis, endarteritis, and fibrosis ensue which lead to mucosal ulceration, caseation necrosis and narrowing of intestinal lumen[82]. Regional lymph node involvement occurs by lymphatic spread.

In a review of 596 patients with abdominal TB[3], the highest incidence of TB was noted in the GIT and in the peritoneum, followed by mesenteric lymph nodes. Within the GIT, the ileocecal area was the most common site of involvement. Infact, disease of the jejunoileum and ileocecal areas together comprised > 75% of cases, with the disease in the colon was found in 12% of the cases [83-86].The predilection of the bacillus for the ileo-cecum is attributed to three factors: 1) relative physiologic stasis of the area 2) the high rate of absorption with more complete digestion; and 3) the abundance of lymphoid tissue in ileocecal region.

Pathology:

Hoon et al [87]originally classified the gross morphological appearance of the involved bowel into ulcerative, ulcerohyperplastic and hyperplasic varieties. Tandon and

Prakash [88] described the bowel lesions as ulcerative and ulcerohypertrophic types.

Ulcerative form has been found more often in malnourished adults, while hypertrophic form is classically found in relatively well nourished adults. The bowel wall is thickened and the serosal surface is studded with nodules of variable size. These ulcerative and stricturous lesions are usually seen in the small intestine. In the less common hypertrophic form, inflammatory response and reactive tissue produce a multinodular mucosal pattern resembling neoplastic masses. The ulcero-hypertrophic pattern, most commonly seen in ileo-cecal region may produce "cobblestone" appearance [14, 88, 89]. The patient often presents with a right iliac fossa lump constituted by the ileocecal region, mesenteric fat and lymph nodes.

Adjacent tuberculous adenitis can cause colonic traction diverticula with narrowing, local fixation, and sinus tract development [14]. Other characteristics of tubercular intestinal lesions include increased mesenteric fat and mesenteric adenopathy with caseation, which grossly resemble Crohn's disease. Rarely colonic TB can present as diffuse tuberculous colitis which must be differentiated from inflammatory bowel disease (IBD), because steroid treatment can be lifesaving in IBD and lethal in ITB [90].

Tuberculous granulomas are initially formed in the mucosa or the Peyer's patches. These granulomas are of variable size and characteristically tend to be confluent, in contrast to those in Crohn's disease. The presence of central caseation is the hallmark of granulomas caused by tuberculosis [88]. Granulomas are often seen just beneath the ulcer bed, mainly in the submucosal layer. Submucosal oedema or widening is inconspicuous. Tubercular ulcers are relatively superficial and usually do not penetrate beyond the muscularis [88]. They may be

single or multiple, usually 3-6 mm in diameter, with an irregular margin and usually present as transverse lesion parallel to each other. This orientation is related to the arrangement of the submucosal lymphatic structures except when a Peyer's patch alone is involved resulting in a longitudinal orientation .The intervening mucosa is usually uninvolved. These ulcers are usually transversely oriented in contrast to Crohn's disease where the ulcers are longitudinal or serpiginous [91]**.** These circumferential 'girdle ulcers', usually cicatrize during healing and form strictures. Occlusive arterial changes may produce ischemia and contribute to the development of strictures[92]. Endarteritis also accounts for the rarity of massive bleeding in cases of intestinal tuberculosis. Shah et al [93] correlated findings on barium studies and superior mesenteric angiography in 20 patients. Angiograms were abnormal in all and showed arterial encasement, stretching and crowding of vessels, and hypervascularity. Patients with strictures had occlusion of the vasa recta, while ulcerated lesions had hypervascularity. In long-standing lesions there may be variable degree of fibrosis of the bowel wall, which extends from submucosa into the muscularis. Many sections may show only non-specific chronic inflammation and no granulomas. Pulimood [94]et al., described histological changes characteristic of TB and CD. They suggested that multiple (mean number of granulomas per section: 5.35), large (mean widest diameter: 193µm), confluent granulomas often with caseation necrosis are characteristic of TB. Other features were ulcers lined by conglomerate epithelioid histiocytes and disproportionate submucosal inflammation. The features characteristics of Crohn's disease (CD) were infrequent (mean number of granulomas per section: 0.75), small (mean widest diameter: 95µm) granulomas, microgranulomas (defined as poorly organized collections of epithelioid histiocytes), focally enhanced colitis, and a high prevalence of chronic inflammation, even in endoscopically

normal appearing areas. They also described that granulomas larger than 400µm in maximum dimension, more than four sites of granulomatous inflammation per site, caseation, a band of epithelioid histiocytes in ulcer bases and location of granulomas in the caecum favored a diagnosis of TB compared to CD[95.]

Mesenteric lymph nodes may be enlarged matted and may caseate. Characteristic granulomas may be seen only in the mesenteric lymph nodes. This is especially common in patients who have taken antitubercular therapy for some time. The reverse, i.e., the presence of granulomas in the intestine and no granulomas in the draining lymph nodes is rare[87].

Clinical features:

ITB is predominantly a disease of young adults. Two-thirds of the patients are 21-40 years old [96, 97] and the mean age of patients is 30-40 years[96]**.** Although some studies mention female preponderance, it seems that the disease affects both sexes equally. Intestinal lesions are present in only 10% of cases of abdominal TB in children[97]. ITB is characterized by different modes of presentation, *viz* acute (no previous history of obstruction), chronic or acute on chronic (episode of acute obstruction with history of sub acute obstruction).

Most patients have constitutional symptoms of fever with evening rise (40-70%), abdominal pain (80-95%), diarrhea (11-20%), constipation, alternating constipation and diarrhea, weight loss (40-90%), anorexia, malaise and night sweats. Pain can be either colicky due to luminal compromise, or dull and continuous when the mesenteric lymph nodes are involved. Some patients, particularly those with miliary tuberculosis, may have features of toxemia [20]with high fever, tachycardia, anemia and leucocytosis. Patients in India probably because of the social stigma still attached to the disease rarely reveal a family

history of TB, which is reported in about one –third of patients in UK[19, 84]. Peripheral lymph nodes (cervical or axillary) may be involved in 3-10% of the patients [17,22,97,98]. Other clinical features depend upon the site, nature and extent of involvement and are detailed below:

Esophageal tuberculosis

Tuberculosis of the esophagus is a rare and constitutes 0.2% of cases of abdominal tuberculosis[99]**.** The relative rarity is thought to be due to rapid transit time and the vertical, smooth stratified squamous epithelium. Esophageal involvement occurs with a secondary spread from adjacent sites such as lymph nodes, pulmonary, and vertebral tuberculosis [100,101] or retrograde lymphatic spread [100]. Primary esophageal tuberculosis is very unusual[102]. Midoesophagus is the most common site of involvement. Rarely, upper one-third may be involved by direct extension from pharynx and larynx. The commonest presenting symptoms are dysphagia , weight loss , retrosternal pain and coughing on swallowing .The disease usually mimics esophageal carcinoma and extra esophageal focus of tuberculosis may not be evident [103].Rarely , there may be massive hematemesis from an aortoesophageal fistula due to tuberculous aortitis [104].

Barium examination demonstrates extrinsic compression of the enlarged lymph nodes to the esophagus, esophago-bronchial fistula, sinus tract formation, mucosal irregularity, and ulceration [105]. Computed tomography is a more reliable method to determine full extent of the disease into mediastinum [105, 106].

Tuberculosis of stomach

Gastric involvement is very rare and constitutes around 0.2-1% of abdominal tuberculosis. It occurs with a secondary spread from adjacent lymph nodes or hematogenous route. The infrequent involvement of the stomach is due to the relative resistance of the gastric mucosa, high acid content in stomach, lack of lymphoid tissue in the stomach and rapid passage of gastric contents into the intestines. Any part of the stomach can be involved but the usual sites are lesser curvature and antrum[99.] Lesions may be ulcerative or hypertrophic infiltrative type.

Gastro duodenal tuberculosis may mimic peptic ulcer disease with a shorter duration of history and non-response to anti -secretary therapy[107]. Constitutional symptoms may be present in affected individuals. Hematemesis is a common presentation. It may also simulate gastric carcinoma. Chowdhary et al [108] reported the rare concurrence of carcinoma and tuberculosis of stomach in the same patient. Primary gastric tuberculosis has also been reported [99].Patient may present with features of outlet obstruction due to inflammatory changes, fibrosis, or enlarged lymph nodes [109,110]. Caseating granulomas seen on microscopy are usually located in mucosa and submucosa, but rarely extend to the muscularis layer. This may the reason for rarity of free perforation in gastric tuberculosis[99].

Radiological features are nonspecific, mimicking the signs of benign ulcer in the ulcerative form of tuberculosis, and of malignancy in the hypertrophied form. Computed tomography (CT) is very important to delineate the regional lymphadenopathy.

Gastric tuberculosis should be differentiated radio graphically from gastric carcinoma, non-Hodgkin's lymphoma, syphilis, and sarcoidosis. Endoscopic biopsy is indicated to obtain the diagnosis. There is no specific picture of duodenal tuberculosis on endoscopy, and demonstration of granulomas or acid fact bacilli on endoscopic biopsy material is unusual. Because of the lack of accurate clinical diagnosis, most patients end up with surgical intervention, and the diagnosis is made by surgery.

Tuberculosis of duodenum:

Duodenal involvement is extremely rare, occurring in up to 0.2- 2% of the patients with ITB [111]. It may present as duodenal obstruction with narrowing and sometimes fistula due to adjacent lymph nodes. Duodenal narrowing due to enlarged lymph nodes is recognized in the third or fourth part of duodenum.

The largest published series of duodenal tuberculosis reported 30 cases from India [112]. Most patients (73%) had symptoms of duodenal obstruction. In a majority of these cases obstruction was due to extrinsic compression by tuberculous lymph nodes, rather than by intrinsic duodenal lesion. The remainder (27%) had a history of dyspepsia and was suspected of having duodenal ulcers. Patient can present with hematemesis [113,114].Other reported complications by various authors are perforation [115], fistulae (pyeloduodenal, duodenocutaneous, blind) [115], excavating ulcers extending into pancreas[116] and obstructive jaundice by compression of the common bile duct[117].

Barium studies reveal evidence of segmental narrowing. Duodenal strictures are usually short but can involve long segments of the duodenum. A matted mass containing

enlarged lymph nodes and thickened mesenteric root is demonstrated by US or CT[118]. There is no specific picture of duodenal tuberculosis on endoscopy, and demonstration of granulomas or acid fact bacilli on endoscopic biopsy material is unusual. Surgical bypass has been required in the majority of cases to relieve obstruction but successful endoscopic balloon dilatation (TTS balloon, Microvasive) of duodenal strictures has been reported by Vij et al[119] in two cases.

Tuberculosis of jejunum and ileum

Jejunal or ileal involvement, except of the terminal ileum is rarely seen. Nonspecific changes are demonstrated on barium studies and CT [89].

Tuberculosis of the appendix:

In India, tuberculosis is found in 2.3 % of appendicectomies [120]. It is usually secondary to tuberculosis elsewhere in the abdomen: local extension of the disease, lymphatic spread, or peritoneal disease. The rare primary disease of the appendix may present with perforation [121].

Ileocecal tuberculosis:

Colicky, midabdominal and/or right lower quadrant pain , distension, gurgling ,vomiting, feeling of a ball of wind moving in the abdomen , and visible loops and peristalsis which are relieved spontaneously after passage of flatus reflects intermittent partial small bowel obstruction, is the presenting complaint in 90-100% of patients [80,122] . Abdominal examination may reveal no abnormality or a doughy feel. A well-defined, firm, usually mobile mass is often palpable in the right lower quadrant of the abdomen in 25-50 % of

cases. Associated lymphadenitis is responsible for the presence of one or more lumps which are mobile if mesenteric nodes are involved and fixed if para-aortic or iliac group of nodes are enlarged [4] .The most common complication is obstruction due to narrowing of the lumen by hyperplasic caecal tuberculosis, by strictures of the small intestine, which are commonly multiple, or by adhesions. Adjacent lymph nodal involvement can lead to traction, narrowing and fixity of bowel loops. In India, around 3 to 20 percent of all cases of bowel obstructions are due to tuberculosis [4,123,124]. In a large series of 348 cases of intestinal obstruction, Bhansali and Sethna [123] found tuberculosis to be responsible for 54 (15.5%) cases; 33 cases were small bowel and 21 large bowel obstruction. Tandon et al [22] studied 186 patients over 5 yr and observed a change in clinical profile with an increase in patients with more protracted course and subacute intestinal obstruction in recent years.

Tuberculosis accounts for 5 to 9 percent of all small intestinal perforations in India, and is the second commonest cause after typhoid fever [125,126]. Evidence of tuberculosis on chest X -ray and a history of subacute intestinal obstruction are important clues. Pneumoperitoneum may be detected on radiographs in only half of the cases. Tubercular perforations are usually single and proximal to a stricture [92]. Acute tubercular peritonitis without intestinal perforation is usually an acute presentation of peritoneal disease but may be due to ruptured caseating lymph nodes [4,126].

Malabsorption is a common complication. It is the most important cause of malabsorption syndrome in India, next to tropical sprue [4]. In a patient with malabsorption, a history of abdominal pain usually suggests the diagnosis of tuberculosis [127]. Pimparkar and Donde [128] studied 40 patients with malabsorption and divided them into those with and without bowel stricture. They performed glucose and lactose tolerance tests, D-xylose test,

faecal fat and Schillings test for B12 malabsorption and found them to be abnormal in 28, 22, 57, 60 and 63 percent respectively in patients with stricture compared to 0, 0, 8, 25 and 30 percent respectively without strictures. Tandon et al [129] also reported biochemical evidence of malabsorption in 75 percent of patients with intestinal obstruction and in 40 percent of those without it. The cause of malabsorption in ITB is postulated to be bacterial overgrowth in a stagnant loop, bile salt deconjugation, diminished absorptive surface due to ulceration, and involvement of lymphatics and lymph nodes. Minor rectal bleeding in ITB has been described frequently [130,131]; however massive bleeding is a rare manifestation of the disease [132-135]. It has been suggested that intestinal TB increases the capillary vascularity, and small arteries undergo obliterative endarteritis that makes bleeding uncommon [136]

Segmental colonic tuberculosis:

Segmental or isolated colonic tuberculosis refers to involvement of the colon without ileocecal region, and constitutes 9.2 percent of all cases of abdominal tuberculosis and around 15-20% of intestinal tuberculosis [137,138]. It commonly involves the sigmoid, ascending and transverse colon [139]. Multifocal involvement is seen in one third (28 to 44%) of patients with colonic tuberculosis [130,140].The median duration of symptoms at presentation is less than 1 yr [131]. Abdominal pain is the predominant symptom in 78-90 percent of patients and hematochezia occurs in less than one third [140,141]. The bleeding is frequently minor and massive bleeding is less common. Singh et al [131] reported rectal bleeding in 31 percent of patients with colonic tuberculosis, and it was massive in 13 percent. Bhargava et al [142] reported bleeding in 70 percent cases. Overall, tuberculosis accounts for about 4 percent of patients with lower gastrointestinal bleeding [92]. The diagnosis is suggested by barium enema or colonoscopy. Tuberculosis is a great mimicker and the most important differential

diagnosis include Crohn's disease, ulcerative colitis (in case of diffuse colitis), carcinoma of colon, amoeboma, Yersinia infection, gastrointestinal histoplasmosis, ischemic colitis, pseudomembranous colitis and periappendiceal abscess. The coexistence of colonic TB and colonic cancer has been described[143]. Colonic tuberculosis might be complicated by perforation causing peritonitis [144].

Rectal and anal tuberculosis

Rectal tuberculosis is rare [147] and may occur as isolated lesions. Clinical presentation of rectal tuberculosis is different from more proximal disease. Hematochezia is the most common symptom (88%) followed by constitutional symptoms (75 %) and constipation (37%) [141]. The high frequency of rectal bleeding may be because of mucosal trauma caused by stool traversing the strictured segment. Digital examination usually reveals an annular stricture. The stricture is usually tight and of variable length with focal areas of deep ulceration. It is usually within 10 cm of the anal verge [131]. Associated perianal disease is very rare. Excessive fibrosis associated with the rectal inflammation results in an increase in presacral space.

Anal tuberculosis is less uncommon and has a distinct clinical presentation. Most anal and perianal lesions are ulcerative, although lupoid and verrucous forms have been described. There is an association with anorectal fistula [145] and perianal tuberculous abscess [149]. Tubercular fistulae are usually multiple. Most ulcers are shallow with bluish undermined edges. Progression of the ulcers is usually slow. There may be associated inguinal lymphadenopathy [145].Biopsy should differentiate the lesions of Crohn's disease, squamous cell carcinoma, Lymphogranuloma venereum and Syphilis. Dandapat et al [146] reported that

12 out of 15 multiple perianal fistulae were of tubercular origin, as compared to only 4 out of 61 solitary perianal fistulae. Shukla et al [145] reported that in India, tuberculosis accounted for up to 14 percent of cases of fistula in ano. Anal discharge was present in all cases and perianal swelling in one third. Constitutional symptoms were not present in any patient [145]. Anal tuberculosis is also seen in paediatric patients [148].

Diagnosis and investigations:

Despite a high index of suspicion, ITB can be difficult to diagnose. Symptoms are vague, signs are nonspecific and the disease closely mimics many other diseases.

Paustian stated that atleat one of the following four criteria must be fulfilled to diagnose abdominal tuberculosis: (i) A positive culture from enteric, mesenteric or lymphatic tissue (ii) typical findings at surgery with histological evidence of tuberculosis in mesenteric nodes (iii) histological demonstration of caseating granuloma ;(iv) histological demonstration of acid fast bacilli in a lesion[152]. A fifth criterion defined by Logan [149] as indicating "probable tuberculosis" is a favorable response to antituberculous treatment of concurrent tuberculosis. These criteria are rarely present together[153]. These criteria must be considered and the diagnosis substantiated by adequate radiological and histopathological studies.

Laboratory results can be nonspecific or normal. The most common abnormal laboratory finding is an elevated erythrocyte sedimentation rate (50-80%) [20, 97, 98]. Mild anemia is also relatively frequent (50-80%) [20, 97, 98]. Hypoalbuminaemia may suggest malnutrition or malabsorption[84].

Tuberculin skin test: A positive purified protein derivative (PPD) test is found in 70-86% of patients[71]; however this test may has limited usefulness in immunosuppressed

patients. The test has a lower specificity for abdominal (77%) [153] than for pulmonary (84%) tuberculosis[154]. It doesn't differentiate between active disease and previous sensitization by contact or vaccination.

Radiological studies**:** Chest X-ray: It is positive in only 25% of the patients [22]. Evidence of tuberculosis in a chest X-ray supports the diagnosis but a normal chest X-ray does not rule it out. Chest X-ray may show evidence of active or healed tuberculosis. Sharma et al [151] studied 70 cases of abdominal tuberculosis and found evidence of active or healed lesions on chest X-ray in 32 (46%). X-rays were more likely to be positive in patients with ulcerative intestinal types and with acute complications [151]. In Prakash's series of 300 patients, none had active pulmonary tuberculosis but 39 percent had evidence of healed tuberculosis[10].

Plain X-ray abdomen: Plain X -ray abdomen may show enteroliths, features of intestinal obstruction i.e., dilated bowel loops with multiple air fluid levels, evidence of ascites, perforation or intussusception. In addition, there may be calcified lymph nodes, calcified granulomas and hepatosplenomegaly.

Small bowel barium meal: The following features may be seen: mucosal irregularity and rapid emptying (in ulcerative type); hyper segmentation of the barium column ("chicken intestine"), precipitation, flocculation and dilution of the barium (due to malabsorption); stiffened and thickened folds; luminal stenosis with smooth but stiff contours ("hour glass stenosis "), multiple strictures with segmental dilatation of bowel loops; and fixity and matting of bowel loops.

Barium enema: The following features may be seen:

(i) Early involvement of the ileocecal region manifesting as spasm and edema of the ileocecal valve. Thickening of the lips of the ileocecal valve and/or wide gaping of the valve with narrowing of the terminal ileum ("Fleischner" or "inverted umbrella sign") are characteristic.

(ii) Fold thickening and contour irregularity of the terminal ileum, better appreciated on double contrast study.

(iii) "Conical caecum", shrunken in size and pulled out of the iliac fossa due to contraction and fibrosis of the mesocolon. The hepatic flexure may also be pulled down.

(iv) Loss of normal ileocecal angle and dilated terminal ileum, appearing suspended from a retracted, fibrosed caecum ("goose neck deformity").

(v) "Purse string stenosis" - localized stenosis opposite the ileocecal valve with a rounded off smooth caecum and a dilated terminal ileum.

(vi) "Stierlin 's sign " is a manifestation of acute inflammation superimposed on a chronically involved segment and is characterized by lack of barium retention in the inflamed segments of the ileum, caecum and variable length of the ascending colon, with a normal configured column of barium on either side. It appears as a narrowing of the terminal ileum with rapid emptying into a shortened, rigid or obliterated caecum.

(vii) "String sign" - persistent narrow stream of barium indicating stenosis.

Both Stierlin and String signs can also be seen in Crohn's disease and hence are not specific for tuberculosis.

Barium studies are sensitive for ileocecal and colonic lesions [98]. Tandon et al [22] reported false-negative barium studies in 25% of patients. Radiological studies may not always differentiate ITB from Crohn's disease and malignancy.

Ultrasonography:

Barium studies though accurate for intrinsic bowel abnormalities, do not detect lesions in the peritoneum. Ultrasound is very useful for imaging peritoneal tuberculosis. The following features may be seen, usually in combination [29].

(i) Intra -abdominal fluid, which may be free or loculated; and clear or complex (with debris and septae). Fluid collections in the pelvis may have thick septa and can mimic ovarian cyst.

(ii) "Club sandwich" or "sliced bread" sign is due to localized fluid between radially oriented bowel loops, due to local exudation from the inflamed bowel (interloop ascitis).

(iii) Lymphadenopathy may be discrete or conglomerated (matted). The echotexture is mixed heterogenous, in contrast to the homogenously hypoechoic nodes of lymphoma. Small discrete anechoic areas representing zones of caseation may be seen within the nodes. With treatment the nodes show a transient increase in size for 3-4 weeks and then gradually reduce in size. Calcification in healing lesions is seen as discrete reflective lines. Both caseation and calcification are highly suggestive of a tubercular etiology, neither being common in malignancy related lymphadenopathy.

(iv) Bowel wall thickening is best appreciated in the ileocecal region. The thickening

is uniform and concentric as opposed to the eccentric thickening at the mesenteric border found in Crohn's disease and the variegated appearance of malignancy.

(v) Pseudokidney sign - involvement of the ileocecal region, which is pulled up to a subhepatic position.

Computed tomographic (CT) scan:

Ileocecal tuberculosis is usually hyperplasic and well evaluated on CT scan. In early disease there is slight symmetric circumferential thickening of caecum and terminal ileum. Later the ileocecal valve and adjacent medial wall of the caecum is asymmetrically thickened. In more advanced disease gross wall thickening, adherent loops, large regional nodes and mesenteric thickening can together form a soft tissue mass centered on the ileocecal junction [155]. Mural stratification does not occur in any of the cases. In comparison, Crohn's disease has a uniform pattern of wall thickening, which is concentric or largely symmetrical, and ranges from 0.6 to 1.7 cm. Some of patients show mural stratification [164].CT scan can also pick up ulceration or nodularity within the terminal ileum, along with narrowing and proximal dilatation. Other areas of small and large bowel involvement manifest as circumferential wall thickening, narrowing of the lumen and ulceration. In the colon, involvement around the hepatic flexure is common. Complications of perforation, abscess, fistula and obstruction are also seen. Although amebiasis may produce the typical shrunken cecum seen in tuberculosis, small bowel association is very rare with amebiasis. Cecal carcinoma is always limited by ileocecal valve[162].

Tubercular ascitic fluid is of high attenuation value (25-45 HU) due to its high protein content. Strands, fine septae and debris within the fluid are characteristic, but are better appreciated on ultrasonography [155]. Thickened peritoneum and enhancing

peritoneal nodules may be seen.

Mesenteric disease on CT scan is seen as a patchy or diffuse increase in density, strands within the mesentery, and a stellate appearance. Lymph nodes may be interspersed. Omental thickening is well seen often as an omental cake appearance. A fibrous wall can cover the omentum, developing from long standing inflammation and is called omental line. An omental line is less common in malignant infiltration [155].

Caseating lymph nodes are seen as having hypodense centers and peripheral rim enhancement. Along with calcification, these findings are highly suggestive of tuberculosis. In tuberculosis the mesentery, mesenteric root, celiac, porta hepatis and peripancreatic nodes are characteristically involved, reflecting the lymphatic drainage of the small bowel. The retroperitoneal nodes (i.e., the periaortic and pericaval) are relatively spared, and are almost never seen in isolation, unlike lymphoma [155].

Colonoscopy:

Colonoscopy with ileoscopy is an excellent tool to diagnose colonic and terminal ileal involvement, but is still often underutilized. Mucosal nodules of variable sizes (2 to 6 mm) and ulcers in a discrete segment of colon, 4 to 8 cm in length are common. The nodules have a pink surface with no friability and are most often found in the caecum especially near the ileocaecal valve. Large (10 to 20 mm) or small (3 to 5 mm) ulcers are commonly located between the nodules. The intervening mucosa may be hyperemic or normal [130]**.** Areas of strictures with nodular and ulcerated mucosa may be seen. Other findings are pseudopolypoid edematous folds, and a deformed and edematous ileocecal valve. Diffuse involvement of the entire colon is rare (4%), but endoscopically can look very similar to

ulcerative colitis. Lesions mimicking carcinoma have also been described[130, 131,141]**.** The ileocecal angle is distorted and often obtuse. Both sides of the ileocecal valve are usually involved leading to incompetence of the valve, another point of distinction from Crohn's disease.

For better yield, 8-10 colonoscopic biopsies are suggested for histopathology (hematoxylin and eosin staining), staining for acid-fast bacteria (Ziehl-Neelsen stain) and culture (Lowenstein-Jensen medium or BACTEC method). Biopsies should be taken from the edge of the ulcers, some suggest even from the base of the ulcer. However, there is a low yield on histopathology because of predominant submucosal involvement. Granulomas have been reported in 8-48 percent of patients and caseation in a third (33-38%) of positive cases [131]. The yield of acid-fast bacilli stains has been variable in studies. Culture positivity is not related to the presence of granulomas. Endoscopic fine needle aspiration cytology may be positive even when the biopsy has been negative[156].

Microbiological diagnosis:

Microbiological diagnosis of ITB may be difficult; the yield of organisms may be low because extrapulmonary disease is paucibacillary. Mycobacterial culture should be performed in all cases (although results take 6 weeks) because it may be positive even in the absence of a characteristic histological picture.

Radiactive Scintigraphy:

Gallium 67 citrate is superior to Indium 111-labelled leucocytes for detecting areas of tuberculous enteritis[157].

Immunological tests:

Chawla et al[158] reported that an optical density (OD) of 0.81 on ELISA and fluorescent coefficient of 2.56 on soluble antigen fluorescent antibody (SAFA) as cut-off gave positivity of 92 and 83 percent, respectively, with 12 and 8 percent false positives respectively. Bhargava et al [159] used competitive ELISA with monoclonal antibody against 38 kD proteins and found a sensitivity of 81 percent, specificity of 88 percent and diagnostic accuracy of 84 percent. However, ELISA remains positive even after therapy, the response to mycobacteria is variable and its reproducibility is poor. Hence the value of immunological tests remains undefined in clinical practice[92].

Polymerase Chain Reaction (PCR) analysis:

The PCR is a unique method of amplifying tiny quantities of DNA and RNA. It is ideally suited for diagnosis of conditions in which infective organisms are present in very minute quantities to be detected by conventional methods such as staining techniques and culture. It has been that PCR can detect as few as 50 organisms per reaction, which is atleast a five fold lower limit of detection compared to culture. PCR analysis of the involved gastrointestinal mucosa is a useful tool for diagnosis of ITB and it assists in differentiation of ITB from Crohn's disease. Two studies found that the sensitivity, specificity, positive predictive value and negative predictive value of PCR assay on tissue specimens in differentiating ITB from Crohn's disease were 21-64.1%, 95-100%, 92-100%, and 28-68.2%, respectively[160, 161]. In a PCR study done on fecal samples of subjects including treated and untreated ITB, smear positive pulmonary TB and controls, the sensitivity, specificity,

positive predictive value and negative predictive value of fecal PCR were 88.8%, 100%, 100%, and 93.7%, respectively[165].

Ascitic fluid examination:

The ascitic fluid in tuberculosis is straw coloured with protein >3g/dl, and total cell count of 150-4000/ µl, consisting predominantly of lymphocytes (>70%). The ascites to blood glucose ratio is less than 0.9650 and serum ascitic albumin gradient is less than 1.1 g/dl.

The yield of organisms on smear and culture is low. Staining for acid-fast bacilli is positive in less than 3 percent of cases. A positive culture is obtained in less than 20 percent of cases, and it takes 6-8 weeks for the mycobacterial colonies to appear. However Singh et al[167] in an earlier study cultured 1 litre of ascitic fluid after centrifugation and obtained 83 per cent culture positivity. Finding an ascitic fluid/blood glucose ratio of less than 0.96 may be useful for distinguishing tuberculosis from other causes of ascites [166].

Adenosine deaminase (ADA) is an aminohydrolase that converts adenosine to inosine and is thus involved in the catabolism of purine bases. The enzyme activity is more in T than in B-lymphocytes, and is proportional to the degree of T cell differentiation. ADA is increased in tuberculous ascitic fluid due to the stimulation of T-cells by mycobacterial antigens. ADA levels were determined in the ascitic fluid of 49 patients by Dwivedi et al[168]. The levels in tuberculous ascitis were significantly higher than those in cirrhotic or malignant ascitis. Taking a cut off level of 33 U/L, the sensitivity, specificity and diagnostic accuracy were 100, 97 and 98 percent respectively[168]. In the study by Bhargava et al[169], serum ADA level above 54U/L, ascitic

fluid ADA level above 36 U/L and a ascitic fluid to serum ADA ratio > 0. 985 were found suggestive of tuberculosis[170]. In coinfection with HIV the ADA values can be normal or low. Falsely high values can occur in malignant ascites. High interferon-γ levels in tubercular ascites have been reported to be useful diagnostically[171]. A cutoff level of 3.2 U/ml gave the assay a sensitivity of 93% and a specificity of 98%. Combining both ADA and interferon estimations may further increase sensitivity and specificity.

Laparoscopic findings:

Bhargava et al[172] studied 87 patients with high protein ascites, of which 38 were diagnosed as having tuberculosis. They found visual appearances to be more helpful (95% accurate) than histology, culture or guinea pig inoculation (82.3 and 37.5% sensitivity respectively). Caseating granulomas may be found in 85-90 percent of the biopsies. The laparoscopic findings in peritoneal tuberculosis can be grouped into 3 categories:

(i) Thickened peritoneum with tubercles: Multiple, yellowish white, uniform sized (about 4 - 5 mm) tubercles diffusely distributed on the parietal peritoneum. The peritoneum is thickened, hyperemic and lacks its usual shiny luster. The omentum, liver and spleen can also be studded with tubercles.

(ii) Thickened peritoneum without tubercles.

(iii) Fibroadhesive peritonitis with markedly thickened peritoneum and multiple thick adhesions fixing the viscera.

Pre-operative diagnosis is difficult even in areas where tuberculosis is common and was obtained in only 40% [98] to 50 %[173] of patients in India, 33% in Kuwait[174] and 25% in UK[84]. Reports of patients who were not diagnosed at life for tuberculosis but were revealed at necropsy have been described. This is most commonly seen in the small intestinal

strictures, which are not amenable to endoscopic or percutaneous biopsy or fine needle aspiration cytology. With advances in endoscopic modalities (enteroscopy), small bowel tuberculosis may be diagnosed at earlier stages at present.

Operative findings are infiltrated thickened and rolled up omentum, increased mesenteric fat wrapping the bowel, short and fibrotic strictures and soft to firm hypertrophic lesions. The opened specimen may show thickened mucosal fold with ulceration and fibrosis. Besides these; ascites, yellow nodules over the visceral and parietal peritoneum (tubercles), adhesions, enlarged and calcified mesenteric lymph nodes may be seen. A frozen section may help to rule out malignancy. A mesenteric lymph node should always be removed because granulomas and caseation are more likely to be found in the nodes than in intestinal lesions[4, 88].

Management:

All patients should receive conventional antitubercular therapy for at least 6 months including initial 2 months of rifampicin, isoniazid, pyrazinamide and ethambutol, followed by rifampicin and isoniazid for next 4 months. A randomized comparison of 6-month short course chemotherapy with a 12 month course of ethambutol and isoniazid (supplemented with streptomycin for the initial 2 wks) was conducted by Balasubramanium et al [175] in 193 adult patients. Cure rate was 99 and 94 percent in patients given short -course and the 12-month regimen respectively. Kim et al, in a randomized comparison in patients with ITB found that 9 months of treatment is as effective as 15 months course of chemotherapy [176].

Acute-on-chronic intestinal obstruction usually responds to conservative management; these patients can be electively investigated and treated accordingly[4].

The surgical treatment of ITB has gone through three phases[177]. Bypassing the

stenosed segment by entero-enterostomy or by ileo-transverse colostomy was practiced when effective antitubercular drugs were unavailable, as any resectional surgery was considered hazardous in the presence of active disease. This practice however, produced blind loop syndrome, and fistulae and recurrent obstruction often occurred in the remaining segments. With the advent of more effective antituberculous drugs, various reports recommended the use of radical procedures in an attempt to eradicate the disease locally. These included right hemicolectomy with or without extensive removal of the draining lymph nodes and wide bowel resections. These procedures were often not tolerated well by the malnourished patient. Moreover the lesions are often widely spaced and not suitable for resection.

The recommended surgical procedures today are conservative; tuberculosis is a systemic disease and cannot be eradicated by surgery alone. A period of pre operative drug therapy is controversial .A segment of bowel bearing multiple strictures or a single long tubular stricture or with almost complete obstruction may merit resection. Resection is segmental with a 5 cm margin.

Tubercular perforations are usually ileal and are associated with distal strictures. Resection and anastomosis is preferred as simple closure of the lesions is associated with a high incidence of leak and fistula formation. Two reports suggest that obstructing intestinal lesions may relieve with antitubercular drugs alone without surgery. Anand et al [179] reported clinical and radiological resolution of tuberculous strictures with drug therapy even in patients with subacute intestinal obstruction. They treated 39 patients with obstructive symptoms using medical therapy. At the end of one year 91 percent showed clinical improvement, 70 percent had complete radiological resolution and surgery was

needed in only 3 cases (8%). Predictors of need for surgery were long strictures (>12 cm) and multiple areas of involvement [179]. Balasubramaniam et al [170] made similar observations. The mean time required for the relief of obstructive symptoms was 6 months, although systemic symptoms improved within 2 months.

Postoperative complications include anastomotic leak resulting in a fecal fistula, peritonitis and intra-abdominal sepsis, persistent obstruction, wound infection and dehiscence[4]. Re-operation may be required during the follow-up for recurrent obstruction due to strictures or adhesions [84, 97].

Mortality rate due to ITB ranges from 4-12 % [20, 97, 98,181] is partly due to the associated malnutrition, anemia and hypoalbuminaemia. Mortality may be higher (12-25%) [4, 97] in the presence of acute complications. Delayed diagnosis and injudicious treatment due either to limited experience and poor understanding of the disease are responsible for mortality.

AIMS OF THE STUDY:

To perform a case control study in patients with intestinal tuberculosis and with matched healthy controls in order:

1. To identify the prevalence of specific risk factors such as diabetes mellitus, HIV infection, family history of tuberculosis, history of BCG vaccination, in patients with intestinal tuberculosis compared to age- and sex-matched control subjects.
2. To determine whether there are specific associations of intestinal tuberculosis with factors connected with childhood hygiene, as well as a history of treatment for intestinal parasitic infections.
3. To determine the frequency of interferon- gamma (IFN-γ) polymorphisms in patients with intestinal tuberculosis compared to appropriately matched healthy controls.
4. To study the clinical and investigation profile of intestinal tuberculosis in our institution from March 2004 to July 2006.

METHODOLOGY:

SUBJECTS:

***Patients**:*

Confirmed intestinal tuberculosis patients included those who had their diagnosis confirmed by colonoscopic biopsies demonstrating caseating granulomas, AFB on smear, or AFB on culture, as well as surgical patients who had surgical resection with a histological diagnosis of tuberculosis made on the resected specimen.

Presumptive intestinal tuberculosis included those patients whose colonoscopic biopsies showed granulomatous or nongranulomatous chronic inflammation of colon or ileum, with or without extra intestinal tuberculosis, and response to anti-tuberculous therapy.

Controls:

Controls included patients with irritable bowel syndrome, acid peptic disease and non-ulcer dyspepsia who were matched for age, sex and geographical region with no history of pulmonary or extra pulmonary TB in the past, in the family or even in the close contacts. These subjects were used for risk factor analysis.

Healthy elderly controls matched for sex and region were used to analyze frequency of interferon–gamma polymorphisms in the general population.

METHODS:

Informed written consent was obtained. A detailed questionnaire including risk factors of intestinal tuberculosis were provided to the patient and controls and all the responses were recorded as given by the patient, and these were maintained in a file. Questionnaire for risk factors concerned with hygiene were demarcated as “during childhood” and “current”. These included residence in village or town, water source for the

household, and availability of toilets. Questionnaire also probed other risk factors like diabetes mellitus, HIV infection, and family history of tuberculosis, history of BCG vaccination, and history of treatment for intestinal parasitic infections. These responses were later entered into a computer for analysis. Relative risks for each of these factors were evaluated .All subjects were investigated as clinically necessary. Clinical and investigation profile of intestinal tuberculosis (ITB) was also analyzed. The questionnaire is provided in the Appendix to this thesis.

A 10 ml sample of blood was drawn by one of the laboratory co-investigators into Vacutainers. DNA was immediately isolated from the whole blood and stored at -20°C pending analysis. Analysis of IFN- γ polymorphisms was done using allele-specific PCR. The genotype was analyzed and comparisons made between patients and controls.

Laboratory analyses

The IFN-γ (+874 A/T) polymorphism was genotyped using allele-specific PCR as described by Lopez-Maderuelo et al [64]. Genomic DNA was amplified in two different PCRs for each polymorphism; each reaction has a generic antisense primer and one of the allele-specific sense primers. One internal control, human growth hormone, was amplified in all the reaction tubes to assess the success of PCR amplification. The amplified PCR products were resolved on 2% agarose gel, stained with ethidium bromide, and documented using a gel documentation system. PCR was performed under the following conditions: initial denaturation at 94°C for 5 minutes; 40 cycles of 94°C for 30 seconds, 50°C for 30 seconds and 72°C for 30 seconds, and final extension at 72°C for 5 minutes.

DNA extraction and mutation analysis was as follows

For DNA extraction the materials required were:

EDTA coated vacutainer tube, centrifuge, plastic Pasteur pipette (sterile), 15ml of self standing centrifuge tube (sterile), RBC lysis buffer, WBC lysis buffer, Proteinase K, 10% Sodium Dodecyl Sulphate (SDS), saturated NaCl, absolute alcohol, Eppendorf tubes (sterile), 70 % ethanol, Tris-EDTA (TE) buffer.

Reagents were prepared in the following manner:

RBC lysis buffer: Dissolve 8.725g of ammonium chloride and 1 g of potassium bicarbonate in 1 liter of water. Check the pH and that should be 7.4. Sterilize the solution by autoclaving and store it at room temperature for a period of 1year.

WBC lysis buffer: Mix 25ml of 0.5M EDTA and 2.19 g of NaCl in 250ml of water and adjust the pH to 8.0 and make the volume to 500ml with water. Sterilize by autoclaving and store it at room temperature for 3 months.

TE buffer (10mM Tris & 0.1mM EDTA): Mix 1ml of 1M Tris (pH 8.0) and 400 □l of 0.25 M EDTA (pH 8.0) and make up the volume to 100ml with water. Sterilize by autoclaving and store in at room temperature for 1 year.

10% SDS: Dissolve 10g of SDS in 100ml of water and heat the solution at 65°C to assist dissolution. Sterilization is not required and store in at room temperature for 6 months.

Proteinase K: Dissolve the lyophilized Proteinase K (Cat no. PK1, Bangalore Genie) in 10ml of sterile water to obtain a concentration of 10mg/ml. Aliquot 500µl volume into Eppendorf tubes and store at -20^0C for a long period.

Saturated NaCl: Dissolve 36.05g of NaCl in 100ml of water and saturate or 6M NaCl solution**.** Sterilize by autoclaving and store in at room temperature for 1 year.

Procedure: Collect blood in EDTA-coated vacutainer tube. Centrifuge the sample at 400rpm for 15min. Three layers will be visible, the top yellow layer is plasma, the middle white layer is buffy coat and the bottom red layer is erythrocytes. The plasma is carefully removed and discarded and buffy coat collected in fresh tube. Ten volumes of RBC lysis buffer is added and incubated at room temperature for 10 minutes. Later the tube is centrifuged at 4000rpm for 10min. The supernatant is discarded and a white pellet will be seen. This is repeated till a clear white pellet is obtained. Add 4.5ml of WBC lysis buffer to the pellet to make a homogenous solution. Add 250µl of 10% of SDS and 100µl of Proteinase K to this solution mix them well and incubate at 37°C for overnight or at 55°C for two hours. Check the lysis, if the lysis is not complete, then add 50µl of Proteinase K and continue the digestion. When the lysis is complete, add 1.5ml of saturated NaCl solution and mix well till the solution turns milky white. Centrifuge this solution at 4000rpm for 15min and collect the supernatant in a fresh tube. To the supernatant add two volumes of absolute ethanol and mix gently, a white thread like structure will be seen which reaches the top of the solution. Collect this thread like structure is in a fresh Eppendorf tube containing 1ml of 70% ethanol, using a sterile pipette tip. Tap the tube very well to remove the excess salt adhering to the precipitate. Remove the precipitate using a pipette tip and air-dry it. When the precipitate turns transparent, transfer it into an Eppendorf tube containing 200-300µl of TE buffer. Dissolve the DNA by incubating at 37°C for 2 hour or 65°C for 30minutes and store in deep freezer (-20°C) for long -term storage or in the fridge for short term.

PCR analysis was done using the primers used in the study by Lopez et al. Primers (sense) used for IFN –gamma A and IFN-gamma T alleles were 5'- ttc tta caa cac aaa atc aaa tca-3' and 5'-ttc tta caa cac aaa atc aaa tct - 3' respectively with polymerized gene product size of 261bp. Sense and antisense primers used for internal controls were 5'-gcc ttc caa cca ttc cct ta-3' and 5'-tca cgg att tct gtt gtg ttt c-3' respectively.

Sample size:

Using appropriate equations, we calculated a sample size of 100 with 50 each in intestinal tuberculosis and control group which was required to study the association between IFN-γ polymorphisms and intestinal tuberculosis with an Odds ratio of 3.5, with 80% power at 5% level of significance, the event rate in control being taken as 36.7%.

Statistical analyses:

For statistical analysis we used the SPSS (version 11). For each of the parameters that are included, relative risks and their confidence intervals were calculated between patients and controls. Significance of the association was calculated using the Chi square test and P value of < 0.05 was considered statistically significant

RESULTS

Demographic characteristics of the subjects

a. Intestinal tuberculosis patients:

The mean age of these patients was 35.56 years, and ranged from 15 years to 61 years. 20 of the patients were females and 30 were males. The age and sex distribution is shown in Table I.

Table I. *Distribution of ITB patients by age and sex*:

Age (years)	Male	Female
11-20	3	3
21-30	7	7
31-40	8	4
41-50	7	2
51-60	4	4
61-70	1	0

50 healthy age- and sex-matched controls were studied for the epidemiologic associations with hygiene and other behaviors. Their ages ranged from 17 years to 61 years (mean 36.38 years). 20 of these were females and 30 were males.

In addition, 50 elderly sex- and region-matched control subjects were studied in order to determine associations of ITB with genetic polymorphisms. 20 were females and 30 were males. Their ages ranged from 60 years to 81 years (mean age 63.5 years).

Epidemiological associations and risk factors:

a. Place of residence, domestic water supply and toilet availability: These are all factors that determine the level of domestic hygiene. Specific infections such as helminth infections (associated with less domestic hygiene) have been postulated to be associated with higher incidence of clinical tuberculosis; hence these factors were examined.

Table II. Putative factors associated with hygiene and their association with ITB.

Risk factors	ITB	Controls	P value	RR	95%CI
Childhood residence					
Village	16	31	0.0048[@]	0.51	0.32-0.81
Town	32	11			
City	2	8			
Current residence					
Village	14	18	0.52[@]	0.77	0.436-1.38
Town	33	22			
City	3	10			
Childhood water source					
Piped water	34	5	0.0001[#]	6.8	2.8-15.9
Tube well	12	28			
Others	4	17			
Current water					
Piped water	40	16	0.0001[#]	2.5	1.13-3.83
Tube well	10	24			
Others	0	10			
Childhood toilet					
None	11	26	0.0035[$]	0.42	0.23-0.76
Shared	3	5			
One/more	36	19			
Current toilet availability					
None	3	8	0.124[$]	0.46	0.19-1.11
Shared	3	5			
One/more	44	37			

[@]*Town and city grouped together and Fisher exact test done to compare residence in village with residence in town/city.* [#]*"Tubewell" and "other" grouped together and Fisher exact test done comparing against Piped water availability.* [$]*"None" and "shared" grouped together and Fisher exact test done comparing against "One or more toilets in house".*

This study revealed that factors associated with increased domestic hygiene levels either during childhood or currently were apparently positively associated with a diagnosis of ITB. Thus, residence in a village in childhood was protective for ITB (RR 0.51, 95% CI 0.32-0.81), while current residence in a village was not protective. Availability of piped water in the household during childhood was a significant risk factor (RR 6.8, CI 2.8-15.9),

while piped water availability currently was also a risk factor (RR 2.5, CI 1.13-3.83) for ITB. Similarly, non-availability of individual toilets in the household during childhood was protective for ITB (RR 0.42, CI 0.23-0.76). [Table II].

b. Other risk factors:

In this study, there was no significant difference between the groups for other socioeconomic and risk factors including education, immunosuppression, alcohol, smoking, BCG vaccination, and anti-helminth treatment (Table III).

Table III. Risk factors that could be associated with ITB

Risk factors	ITB % (n=50)	Control % (n=50)	P value
Education	100	94	0.665
Past history of TB	10	0	0.022
Family history of TB	8	0	0.041
Immunosuppressive therapy	2	0	0.315
High risk behaviour	0	0	0
Alcohol use	14	10	0.538
Smoking	12	8	0.505
BCG vaccination	98	98	1
Treatment of intestinal parasites	36	36	1

c. Interferon-gamma polymorphisms:

As shown in Table IV and depicted in figure 1, most of the patients as well as the controls were heterozygous for the IFN-γ polymorphisms. No significant difference was noted between the two groups.

Table IV. Frequency of IFN – gamma polymorphisms among ITB patients and healthy controls.

Subjects	IFN – gamma (+ 874 A/T genotypes)		
	AA (%)	TA (%)	TT (%)
ITB	0	50	0
Age matched healthy Controls	0	50	0
Elderly controls	0	50	0

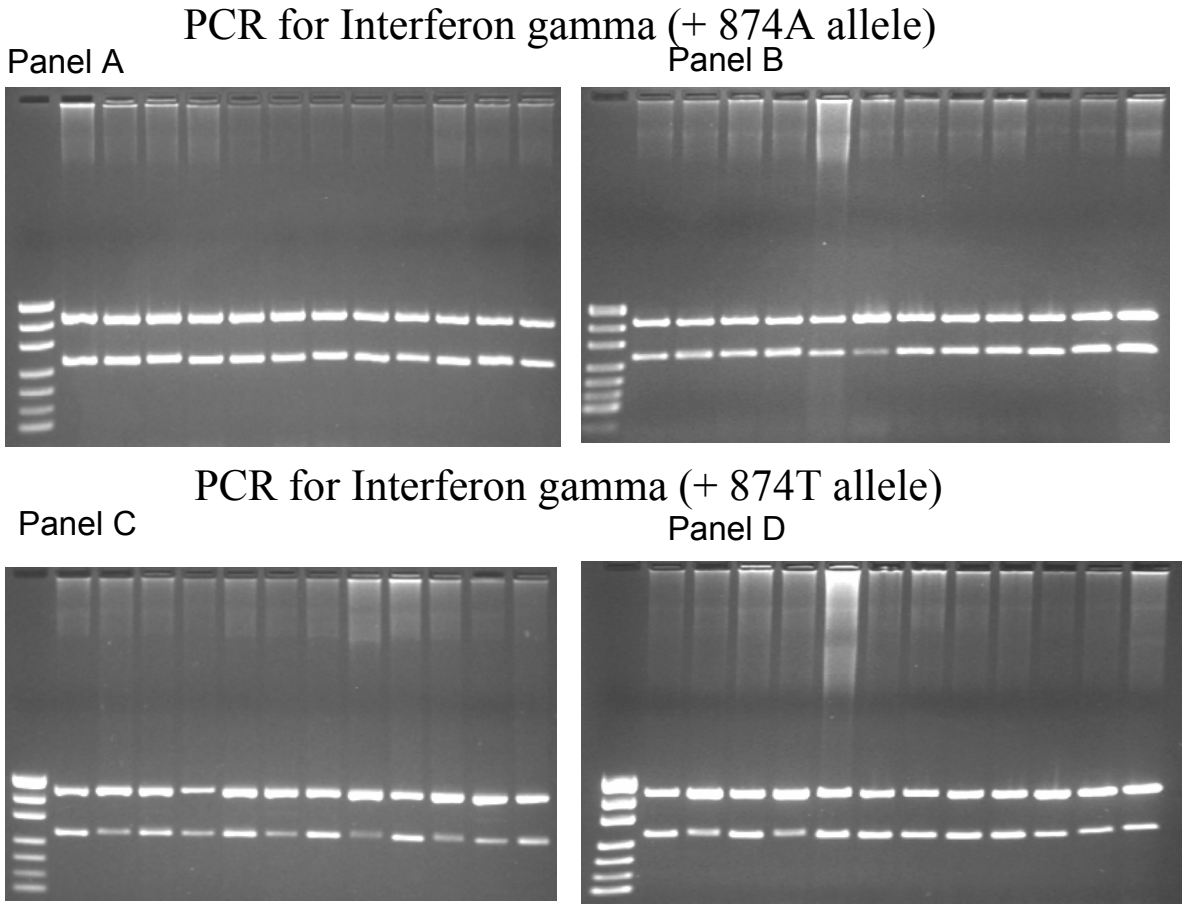

Figure 1.

The above picture shows some of the PCR products of the patients and controls (A & C and B & D) respectively. The bands (i.e., PCR products mounted on 2% agarose gel) are seen in both the groups suggesting that the patients and controls have both A allele and T allele i.e., patients and controls are heterozygous for interferon – gamma (+ 874 A/T) polymorphisms.

Clinical features

1. Location of disease:

Table V shows the disease location by sex of patient in the 50 patients with ITB. When examined according to site of disease involvement, the largest single group among males and females had ileo-colonic involvement (12/30 - 40 % and 9/20 – 45%). There was a trend towards higher involvement of ileo-cecal among males (8/9) and colonic involvement among female (6 /10) patients.

Table V. Location of disease in ITB.

Location	Male	Female
Esophagus	1	0
Stomach and Duodenum	0	1
Ileum	5	2
Ileocecal	8	1
Ileocolonic	12	9
Colonic	4	6
Others	0	1
Total	30	20

2. Clinical presentation of ITB:

Figure 2, shows the clinical presentation of 50 ITB patients: Abdominal pain was the most common clinical presentation (80%).

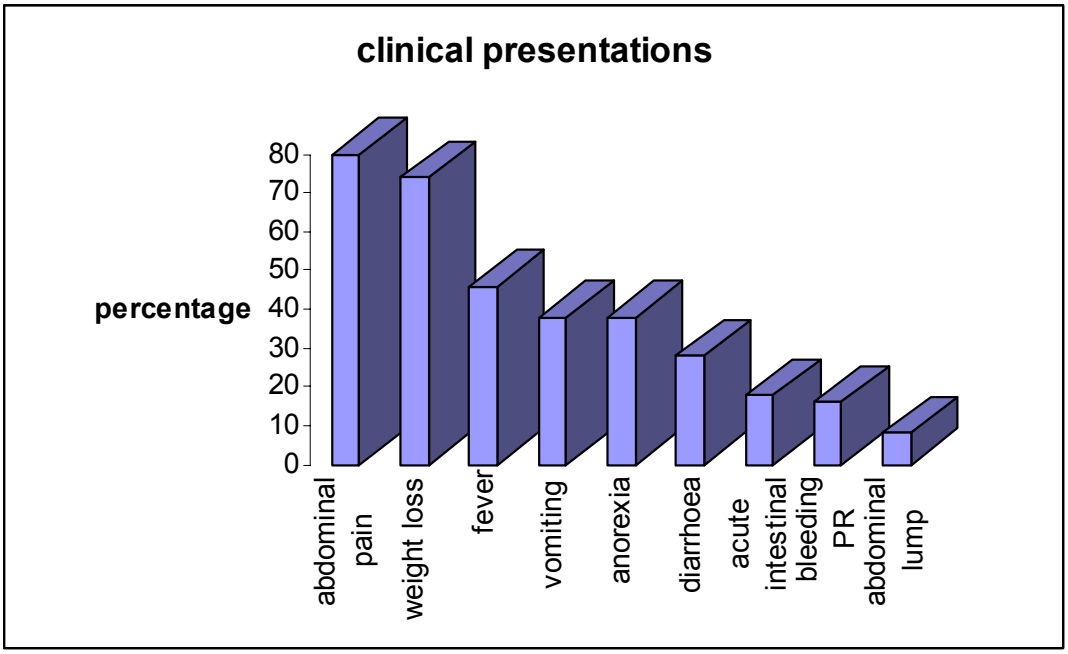

Figure 2: Clinical presentation of intestinal tuberculosis

Table VI shows location of disease (small bowel and colonic) in relation to presentation. Abdominal pain was uniformly distributed.Bleeding per rectum as evidenced by malena / maroon colored stools was more common in ileal involvement alone or with adjacent colonic involvement compared to segmental colonic involvement.

Chronic diarrhea was common in patients with colonic involvement (40%- 8 % of total cases) compared to Ileocolonic (30% - 18 % of total cases) or ileal involvement (0). Subacute intestinal obstruction was common in ileo-colonic involvement (23%).

Table VI: Location of disease (small bowel and colonic) in relation to presentation.

Presentation	Location Ileum and small bowel n = 7	Ileo-colonic n= 30	Colonic n = 10
Fever	3	13	6
Abdominal pain	7	23	9
Vomiting	2	13	2
Diarrhea	0	9	4
Bleeding per rectum	3	5	0
Abdominal lump	2	2	0
Weight loss	5	21	8
Subacute intestinal obstruction	1	7	0
Anorexia	1	12	5

One patient each with esophageal involvement presented with fever, weight loss and dysphagia, gastro duodenal involvement presented with features of gastric outlet obstruction and weight loss; duodeno-colonic involvement with abdominal pain, diarrhea and weight loss.

Mean duration of symptoms: 1.4 years.

3. Physical findings in intestinal tuberculosis:

Figure 3, shows physical findings in 50 ITB patients. Fever was the most common general finding (56%).Palpable mass was the most common per abdominal finding(28%).

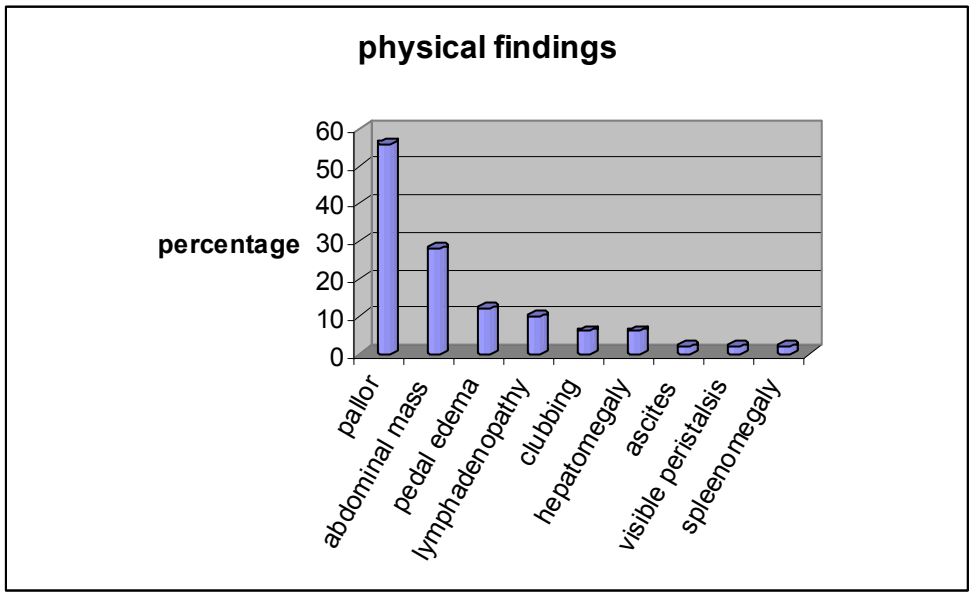

Figure 3: Physical findings in intestinal tuberculosis.

4. Radiological findings in ITB:

Table VII shows radiological findings (USG abdomen and CT abdomen) in 50 ITB patients. Radiological findings were nonspecific and bowel wall thickening is the most common finding in both the modalities (45% and 100%) respectively.

Table VII: radiological findings in intestinal tuberculosis:

Abnormalities	USG abdomen % (n=31)	CT abdomen % (n=6)
Bowel wall thickening	45	100
Omental thickening	16	33
Mesenteric LN	35	66
Ascites	16	0

5. Endoscopic findings in ITB:

Table VIII shows endoscopic findings in 50 ITB patients. Ulcerations and nodularity were most common findings.

Table VIII: Endoscopic findings in 50 ITB patients

Colonoscopic findings	Ileal or small bowel % (n= 4)	Ileocolonic % (n=30)	Colonic % (n=10)
Ulcers	75	70	80
Nodularity	50	83	70
Skip lesions	0	20	0
Stricture	0	9	60
Deformed ileo-cecal valve	0	50	0
Cobblestone	0	3	0
Normal	0	0	10
Pseudopolyps	0	3	10
Growth	0	0	20

Colonoscopy was normal in one patient who was on immunosuppressants (leflunomide) for rheumatoid arthritis and diagnosis was made on segmental biopsies. (Confluent granulomas were seen and repeat biopsies on follow up after 9 months of treatment were normal).

Terminal ileum had ulcerations or nodularity in 46.5% of ileo-colonic involvement. Hence terminal ileal involvement was seen in 36% of the total cases and only caecal involvement

in 4% of total cases. Combined ileocecal lesions were seen in 18% of the patients. Ileo-cecal valve was deformed (stenosed or patulous) in 50% of cases with ileo-colonic involvement.

Esophagus was involved in 2% of the cases. This patient had dysphagia and a midoesophageal ulcer on endoscopy, biopsy revealed granuloma. There was no evidence of pulmonary involvement.Gastro duodenal involvement was seen in 2% of cases. This patient had features of gastric outlet obstruction with large ulcers and nodularity in stomach and duodenum causing obstruction at D1-D2 junction. Endoscopic biopsy confirmed tuberculosis on culture.She had spontaneous perforation at the fundus of the stomach and underwent laparotomy and omental patch closure of gastric perforation with gastrostomy.

6. Surgical findings

Surgery was performed in 8 patients.

Five patients were diagnosed to have TB after surgery, one had presented with perforation, three had features of subacute intestinal obstruction (SAIO) and one had chronic diarrhoea. Three had ileal ulcers and one each had ileo-colonic and duodeno-colonic involvement. Two patients had undergone colonoscopy, but biopsies were inconclusive. One of these patients had duodeno –colonic fistula with granulomas seen in resected bowel and mesenteric lymph node. Two lesions in colon appeared like malignant growths causing luminal compromise.

36% had extra-luminal involvement with omental thickening and / or mesenteric lymphadenopathy in (12%), disseminated tuberculosis (20%) with tuberculous cervical lymphadenitis (6%), pulmonary involvement in 12% i.e., bronchial involvement (2%), pleural

effusion (4%) and parenchyma in 6%; hepatic and thoracic spine involvement in 2% each of cases.

11 / 41 patients (26.8%) of the cases had pulmonary involvement with active TB in 12.2 % and healed TB in 14.6%.

Hemoglobin was < 8 in 9 patients and > 8 and < 10 gm/dl in 9 patients i.e., <10gm/dl in 18 patients.

26/ 48 patients had hypoalbuminaemia (< 3.5 g/dl). Serum albumin was <2.5g/dl in 14 patients and <1.5g/dl in 2 patients respectively. 12 patients had only hypoalbuminaemia without significant anemia (serum albumin < 3.5 g/dl and Hemoglobin > 10 gm/dl).

Table IX correlates hypoalbuminaemia with disease location. As shown in the table, there is no significant difference between different locations.

Table IX: Hypoalbuminemia and disease location:

Location	Number of patients with serum albumin < 2.5gm/dl
Small bowel / ileal	2
Ileo-colonic	6
Colonic	5
Others	1

7. Histopathology:

ITB was confirmed in 80% of the cases and was probable in 20 % of cases.

Granulomas were found in 76 % of cases, with caseation in 28% and confluent in 48 %. AFB was seen on smear in 28 % of biopsy specimens. Chronic nonspecific colitis was seen in 20 % of cases.

8. Microbiological findings

AFB smear and culture were positive in 41.3% (19/46 cases- 18 were culture positive and 2 were smear positive) of the cases where biopsy specimens were sent for microbiological study. Biopsy specimen was not sent for microbiologic study in 4 (8 %) patients. Smear was positive in 2 cases and was helpful in diagnosing in one case where culture was negative.

AFB smears and / or culture was thus helpful in making the diagnosis in 5 (10 %) of the patients where histopathology was inconclusive.

Stool PCR for AFB was positive in 11/ 13 patients out of which 4 had features of healed TB on chest X-ray. None of them had active pulmonary tuberculosis.

9. Response to treatment:

Most (70%) of our patients had 9 months of treatment, 6 months in 24% and 12 months in 6 %.

40% were cured of the disease, 34 % were still under treatment and 26 % had lost to follow up.

Figure 4, shows complications of ITB like SAIO, perforation, bleeding and fistula were seen in 20%, 8%, 4 % and 2 % respectively. One of the patients had bleeding while on treatment and other had it 2 weeks after surgery with ulcers at the anastomotic site which responded to conservative treatment.

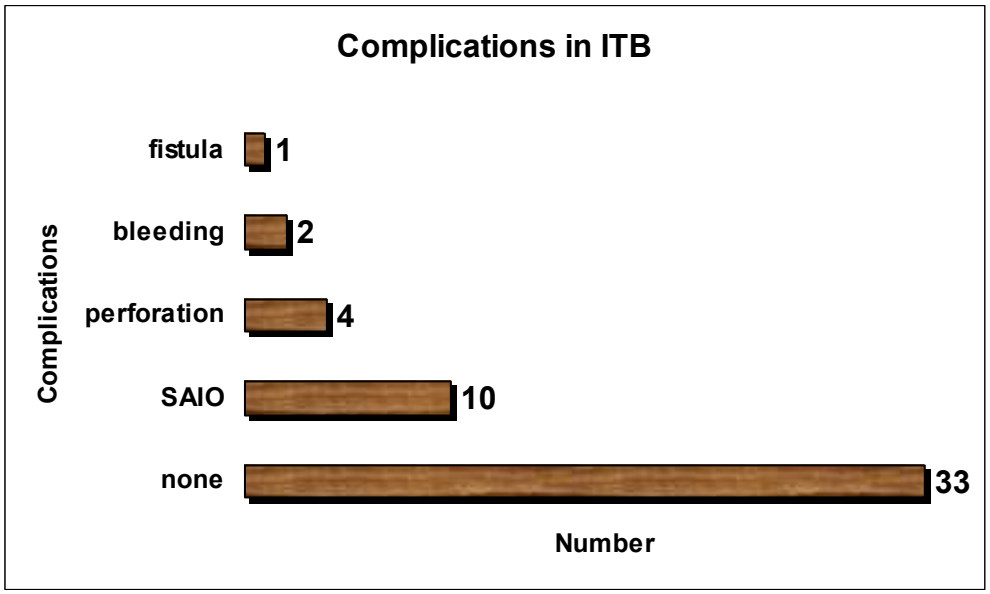

Figure 4: complications in intestinal tuberculosis.

DISCUSSION:

Tuberculosis is common in developing countries. Poor socio-economic status, poor sanitation and the recent upsurge of HIV infection are thought to enhance the susceptibility to tuberculosis in India. Although pulmonary tuberculosis is very common, intestinal tuberculosis accounts for only a small proportion of the total cases of tuberculosis. The risk factors for intestinal tuberculosis (ITB) are not known. In addition, there is now increasing incidence of Crohn's disease, the other granulomatous bowel disease that mimics tuberculosis. In Crohn's disease, it is thought that hygiene status in childhood is responsible for the emergence of intestinal inflammation. Thus, Gent et al found that Crohn's disease was more common in subjects whose first houses had a hot-water tap and separate bathroom[188]. This connection between Crohn's disease and better hygiene in childhood is ascribed to an effect of gastrointestinal infection on immune conditioning of the gastrointestinal tract. The relationship between intestinal tuberculosis and childhood hygiene is not known. It is commonly considered that tuberculosis is more rampant where the level of domestic hygiene is less. Surprisingly, the present study found that parameters like living in a village during childhood, lack of piped drinking water in childhood and lack of toilet facilities in childhood - all of which reflect poor childhood hygiene – actually appeared to be protective against ITB. These findings suggest that immune conditioning by gastrointestinal infections during childhood may protect against the development of ITB.

Studies done by Bentwich Z et al [65] and Elias D et al [66] suggested that there was a strong positive association between TB and intestinal helminth infection. Helminths are usually found to activate Th2-type immune responses and to down-regulate Th1-type responses. The latter are responsible for production of interferon-gamma which is usually considered essential for

containment of tuberculous infection. However, the present study did not find any significant association between intestinal helminth infection or treatment for parasites and the occurrence of intestinal tuberculosis.

There is some evidence that host genetic factors play a role in susceptibility to tuberculosis. Kallmann and Reisner[28] found an appreciably high concordance of pulmonary TB in monozygotic compared to dizygotic twins. Humans defective in genes for IFN-gamma or the IFN-gamma receptor are prone to serious mycobacterial infections, including tuberculosis [37, 38]. Dolores Lopez et al [64]and Manada Rossow et al[39] found that polymorphisms in the gene for IFN-gamma (+ 874 A/T) were associated with increased risk of pulmonary tuberculosis in Spanish and Cambodian population respectively. In a study, IFN-gamma production was most severely depressed in patients with moderately advanced and far advanced pulmonary disease suggesting functional significance of genetic polymorphisms in these cytokines [43]. In our study there was a high level of heterozygosity for IFN-gamma gene polymorphisms in the community and the prevalence of these polymorphisms did not significantly differ in ITB. Although this was a small study in terms of numbers of patients studied, this suggests lack of a major role for IFN-gamma gene polymorphisms in the development of ITB in Indians. It is possible that other genetic factors or environmental factors may play a predominant role in genesis of ITB.

Though HIV was screened in 80% of the cases, none of the patients was seropositive. 13% and 16.6% of the patients with gastrointestinal tuberculosis in two series from India had HIV infection [182,183]. Low rates of HIV positivity in India among gastrointestinal tuberculosis cases probably reflect the high endemicity of TB even without HIV infection.

Age at presentation ranged from 15 to 61 years, highlighting the fact that no adult age group is immune to intestinal tuberculosis. The maximum number of cases, however, was seen in

the younger age group 21-40 years (52 % of cases) with a mean age of 35.56 years. These results are similar to other Indian studies [96,131,182]. The mean age was slightly lower than the mean age of 40 years reported by Chang et al from Taiwan [191].This may be attributed to the higher prevalence of and the earlier age of exposure to TB in our country.

There was slight preponderance of male sex (M:F = 3:2) which is in accordance with other studies[131,182].This may be due to the fact that males have more access to the health system in India compared to females. Earlier workers have observed the disease with variable female[96] preponderance.

Abdominal pain, weight loss and fever were the most common clinical presentation (80%, 46% and 74 % respectively) and abdominal mass (28 %) was the most common clinical finding. Almost similar findings were seen in other studies[131, 137,182,184,189]. As in our study, none of the clinical features were pathognomonic of ITB. Weight loss could be the result of catabolism subsequent to infection, malabsorption secondary to small bowel overgrowth, increased bile salt losses from ileum, and post prandial abdominal discomfort[137].Most of the patients with bleeding (87%) had ulcerations in ileal (50%) and ileo-colonic areas (37%). In a study[96], bleeding due to ulceronodular lesions in ileo-cecal region was noted in only 4% of cases.

Ileo-colonic i.e., ileum with contiguous colonic involvement including cecum (60 %) was the most common site of involvement in our study. In a study by Kyoung Mee Kim et al[192], ileo-colonic involvement was seen in 55% of the cases. Ileocecum was involved in 18 % of the cases as compared to other studies with 20 % [182], 31 % [131], 42% [80]. The predilection of the bacillus for the ileo-cecum is mainly attributed to three factors: 1) relative physiologic stasis in the area 2) the high rate of absorption with more complete digestion; and 3) the abundance of lymphoid tissue in ileocecal region.

Oesophageal, gastroduodenal and duodeno-colonic involvement was seen in one patient each (2% each). The higher incidence of small intestinal TB in previous studies was probably due to inclusion of reports from surgical series and presumptive diagnosis based on radiological studies of small bowel series .The low incidence of small bowel involvement in our study could be due to the fact that endoscopic confirmation (histopathological and microbiological) at sites other than small bowel did not warrant further evaluation of small bowel. These were similar to the findings in recent studies [80,182].

Radiological findings were non-specific. The results obtained on CT scans are comparable to USG findings in other studies[182]. Ileocecal valve was deformed in 30% of the total cases and ITB was confirmed in 80% of these findings. In a retrospective study[182], ileocecal valve was abnormal in 20% of the cases and all of them were found to have TB on basis of histopathologic or microbiologic methods. .

Endoscopic features of ITB are also not pathognomonic, and so required confirmation by biopsy. Common colonoscopic findings were ulcers (68%), nodularity (68%), skip lesions (15%), deformed ileo-cecal valve (30%), stricture (20%), mass like appearance (4%), pseudopolyps in 2% and cobblestone appearance in 2%. In other studies the findings included ulcers (28-92%), nodularity(56-80%), deformed ileo-cecal valve (40-55%), stricture (12-27.5%)[131,160,189,192], pseudopolyps (70%)[160] One patient had normal colonoscopy but segmental biopsy revealed granulomas which responded to a course of ATT as evidenced by normal colonoscopy and biopsy on follow up. Mishra et al [190], in a series of 130 patients with colonic TB, suggested that dilatation of colonic stricture was helpful in detecting the abnormalities in proximal colon and terminal ileum and in confirming the diagnosis of ITB in 50 % of patients with colonic stricture.

ITB was confirmed in 80% of the cases and were probable in 20% of cases. In a retrospective series of 260 cases, 66.5% of GITB were confirmed and 29.6% were probable TB. Confirmed diagnosis was obtained in 100% of cases occurring in the upper gastrointestinal tract, 66% of cases in the ileocecal region/colon and 40% of cases that had small bowel involvement[182] In a series from Lancashire, UK**,** a 94% confirmation was achieved in cases of abdominal TB[84].The high percentage of use of surgical technique and necropsy diagnosis in both series from a nonendemic areas are the reasons for high rate of confirmed diagnosis.

Granuloma was found in 76 % of cases with caseation in 28% and confluent granulomas in 48 %. AFB was seen in 28 % of biopsy specimens. Chronic nonspecific colitis was seen in 20 % of cases. In series from Singh et al [131], Nikhil at al [182] and Alvares et al[184] caseating granulomas were seen in 19%, 61%, 66% of cases and AFB staining in 0, 5%, 15.6% cases. Chronic colonic inflammation was seen in 30% of Alvares's series[184]. In our study, the yield from ulcers were higher because the biopsy material was subjected to microbiology (smear and culture), in addition to histological studies which was also the reason in other studies[182].

AFB smears and/or culture was positive in 41.3% (38% of total cases) of the biopsy specimens sent for microbiological analysis (19/46). Smear was positive in 2 cases and was helpful in diagnosing in one case where culture was negative. The yield of positive cultures was seen to be greater in tissue with caseation necrosis, though organisms were also recovered from tissues showing non-caseating granuloma and non-specific inflammation. The intestinal tissue gave more positive cultures (41%) than did lymph nodes (14%). Vij et al [17] and Bhargava et al[130], reported positive cultures in 40% of endoscopy biopsy specimens although acid-fast bacilli were not seen in any of the endoscopy specimens of the first series. Hence routine culture of biopsy tissue increases the diagnostic yield. In a series by Shah et al[137], none of them were culture

positive. In the present study, AFB smears and / or culture was helpful in making the diagnosis in 5 patients where histopathology was inconclusive. A combination of histology and culture of the biopsy material can be expected to establish the diagnosis in over 60-80 percent of cases[137, 153]. Stool PCR for AFB was positive in 11/13 patients out of which 4 had features of healed TB on chest X-ray. None of them had active pulmonary tuberculosis.

36% had extra-luminal involvement with omental thickening and / or mesenteric lymphadenopathy in (12%) , disseminated tuberculosis (20%) with tuberculous cervical lymphadenitis (6%) , pulmonary involvement in 12% i.e., bronchial involvement (2%), pleural effusion (4%) and parenchyma in (6%); hepatic and thoracic spine involvement in 2% each of cases. 11 / 41 patients (26.8%) of the cases had pulmonary involvement with active TB in 12.2 % and healed TB in 14.6%. This is in comparison with other studies[22].

8 patients (16 %) underwent surgery and was diagnostic 5 (10 %) , therapeutic 3 (6 %) , diagnostic and therapeutic in 5 (10 %) cases . In our study, lower incidence of surgical modality as a diagnostic procedure may be due to the higher yield of colonoscopic biopsies.

Complications like subacute intestinal obstruction, perforation, bleeding and fistula were seen in 20%, 8 %, 4 % and 2 % respectively while on treatment. Subacute intestinal obstruction was managed conservatively in one and the other underwent ileal stricturoplasty and limited right hemicolectomy. Two patients had bleeding, one from the ulcers in ileum and other at the ileo-colonic anastomotic site 2 weeks after right hemi-colectomy done elsewhere. Both were managed conservatively and blood transfusions were required in the second patient. Three patients had perforations, two were ileal and one was from stomach. One patient had multiple ileal perforations (4 in number) and he underwent resection of the involved ileal segment and ileostomy with plan for ileostomy closure at a later date. Other patient with ileal perforation

underwent omental patch closure of the perforation with ileostomy followed by ileostomy closure and limited right hemicolectomy for ileo-cecal junction stricture after 2 months. Bhansali [4]reported that small intestinal strictures were multiple in 71 out of 119 patients; as many as 12,16 and 19 strictures have been reported in a single patient. One patient in our study with gastric perforation underwent omental patch closure of the perforation with feeding gastrostomy.One patient with fistula underwent left hemicolectomy and end colostomy with repair of duodeno-colonic fistula. In a study by Prakash et al[20]; out of 300 patients with ITB between 1959 to 1977, there was a transition from radical hemicolectomy, performed in initial 107 patients, to limited ileo-colonic resection in 88 later patients. Pujari et al [177] suggested that strictures which reduce the lumen by half or more and which cause proximal hypertrophy or dilation needs to be treated by strictureplasty [177] which involves a 5-6 cm long incision along the anti -mesenteric side, which is closed transversely in two layers. Katariya et al [178] reported stricturoplasty in pyloroduodenal and ileocecal lesions.

Out of the 8 patients who had undergone surgery, caseating granulomas were seen in all specimens with mesenteric lymphnodes and AFB bacilli were seen in two of the lymph nodes. Hoon et al[37], suggested that caseating granulomas are frequently seen in mesenteric lymph nodes even though they are absent in intestinal specimens. This is most commonly seen if the patient is on anti-tubercular treatment.

Most (70%) of our patients are on 9 months , 24% on 6 months and 6% on12 months of treatment. Two studies done earlier have shown that short course treatment is as effective as long term treatment [175,176].

CONCLUSIONS

1. A case-control study showed that several factors concerned with domestic hygiene during childhood were strongly associated with a diagnosis of intestinal tuberculosis. These included:
    a. Living in a town or city (versus a village) during childhood
    b. Availability of piped drinking water in childhood
    c. Presence of toilets in the house in childhood

    These findings suggest that immune conditioning of the gastrointestinal tract during childhood by poor domestic hygiene may protect against intestinal tuberculosis.
2. There was high level of heterozygosity for IFN-gamma polymophisms in the community, and the prevalence of these polymorphisms did not significantly differ in ITB.
3. In this small series, the usual risk factors for intestinal tuberculosis, including HIV infection, were not detected.
4. Male:Female ratio was 3:2 i.e., male predominance.
5. Mean age of presentation was 35.56 years.
6. Abdominal pain was the most common clinical presentation and abdominal mass was the most common clinical finding.
7. Disease distribution was oesophageal (2%), gastroduodenal (2%), duodeno-colonic (2%), ileal (14%), ileocolonic (including ileocecal) in 60 % and colonic in 20%.

8. Colonoscopic ulcers and nodularity were most common findings. Yield of colonoscopic specimens in diagnosis was high.
9. Diagnosis was confirmed in 80% of the cases using histopathological and microbiologial methods.
10. Surgery was infrequently needed, mainly to treat complications.

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Case report form

RISK FACTORS FOR INTESTINAL TUBERCULOSIS

Name : Age : Sex: M / F
Hosp.No. : Occupation ;
D.O.B. :
Address :

District and state of residence:

Tel. :
E-mail :
Religion : Hindu Christian Muslim Others (specify)

	Age 0-5	Current
Area of residence	Village	Village
	Town	Town
	City	City
	Urban slum	Urban slum
Predominant water source	Piped water	Piped water
	Tube well	Tube well
	River	River
	Lake	Lake
	Tank	Tank
	Others (specify)	Other (specify)
Toilet facilities	None in house	None in house
	Shared with other families	Shared with other families
	Single toilet	Single toilet
	Multiple toilets in house	Multiple toilets in house

Education: None I-V Std. VI-X Std. +2 Graduate Postgraduate

Other history:

Pulmonary or other TB	No	Yes (details)		
Diabetes mellitus	No	Yes (details)		
Immunosuppressive therapy	No	Yes (details)		
Risk behavior	Never	Occasional	Frequent	
Alcohol use	Never	Occasional	Regular	Ex-user
Smoker	Never	Occasional	Regular	Ex-smoker
Family h/o tuberculosis	Sibling	Parent	Grandparent	Others

BCG vaccination	No	Yes
Treatment for intestinal parasites	No	Yes

History:	***Present***	***Absent***
Fever		
Abdominal pain		
Vomiting		
Diarrhea		
Bleeding PR		
Abdominal lump		
Weight loss		
Acute intestinal obstruction		

Clinical Examination:

Pallor
Icterus
Pedal edema
Clubbing
Lymph nodes
Ht. (cm)
Wt. (Kg)
BMI
Abdomen:
- Distension
- Peristalsis
- Mass
- Liver
- Spleen
- Ascites

Other systems

Investigations: Only clinically indicated investigations will be done

Hb:
MCV:
Retics:
WBC TC: DC: N L M E B BF
Platelets:
ESR:
Fasting blood sugar:
Post-prandial blood sugar:
S. creatinine:

Liver function tests:
HIV:
Stool occult blood:
Stool parasite:
Mantoux test:

Chest X-Ray:

Ultra sonogram of abdomen:

Barium meal follow through:

CT scan:

Gastroscopy:

Colonoscopy:

Surgical finings:

Biopsy reports:

AFB Culture:

AFB PCR:

Genotyping for IFN- polymorphism:

Final diagnosis: Confirmed Probable

Site of involvement:

Treatment given:

Response to therapy:

Cured	Did not resolve	Still under therapy
Therapy is continued	Did not follow up	

Duration of treatment (months): 6 9 12 DOTS

Complications:

SAIO	Bleeding	Fistula
Perforation	Nil	